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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/541,094	03/31/2000	Peter H. St. George-Hyslop	1034/1F812-US2	4017

7590 07/16/2003

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EXAMINER
WOITACH, JOSEPH T

ART UNIT	PAPER NUMBER
1632	21

DATE MAILED: 07/16/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

File

Office Action Summary	Application No. 09/541,094	Applicant(s) St. George-Hyslop et al.
	Examiner Joseph Woitach	Art Unit 1632

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Apr 30, 2003*.

2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *42, 47, 49, 50, 52-54, 56-61, 63, and 65* is/are pending in the application.

4a) Of the above, claim(s) *42* is/are withdrawn from consideration.

5) ☒ Claim(s) *47, 49, 50, and 56-59* is/are allowed.

6) ☒ Claim(s) *52, 54, 60, and 61* is/are rejected.

7) ☒ Claim(s) *53, 63, and 65* is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☒ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

This application claims benefit to provisional applications 60/127,452, filed April 1, 1999, and 60/173,826, filed December 30, 1999.

Applicants' amendment filed April 30, 2003, paper number 20, has been received and entered. The specification has been amended. Claims 47, 49, 52-54, 56 and 58 have been amended. Claims 42, 47, 49-50, 52-54, 56-61, 63 and 65 are pending. Claim 42 is withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 10. Claims 47, 49-50, 52-54, 56-61, 63 and 65 are currently under examination as they are drawn to the elected invention of human PAMP nucleic acid sequences.

Applicants are reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

This application contains claims drawn to an invention nonelected with traverse in Paper No. 10. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Oath/Declaration

The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

Applicants argue that the preliminary amendment only indicated a priority claim and that it did not introduce new matter which would require a new oath. See Applicants' amendment, page 10. Applicants' arguments have been fully considered, but not found persuasive.

Examiner notes that the preliminary amendment is directed towards the claim for priority, however the amendment includes the recitation that each of the documents are "incorporated herein by reference" (page 2, preliminary amendment). Upon review of the teachings in the provisional applications and that of the instant application it is found that the disclosures are different, and the incorporation of the material by reference constitutes new matter which was not part of the original specification (see also discussion of priority, below). Therefore, a substitute declaration or oath to correct the deficiencies clearly indicating the application serial number and indicating 'as amended in the preliminary amendment filed March 31, 2000' is required.

Priority

Applicants argue that the present application has support in provisional applications 60/127,452, filed April 1, 1999, because it discloses the processed amino acid sequence and that

the additional 23 propeptide is indicated. Further, the sequence in 60/173,826, filed December 30, 1999, identifies the same sequence as claimed even by the same sequence identifier (SEQ ID NO: 14). Finally, Applicants note that no reference has been provided as prior art. See Applicants amendment, pages 11-12.

Upon review of 60/173,826, Examiner has compared the identity of the sequences disclosed and agrees that the present application has priority to the filing date of December 30, 1999, for SEQ ID NO: 14. With respect to 60/127,452, filed April 1, 1999, Examiner agrees that the specification provides the figurative support for the 23 amino acid propeptide, but not the specific portion of the sequence set forth SEQ ID NO: 14. Because SEQ ID NO: 2 (disclosed in the provisional application) as compared to SEQ ID NO: 14 comprises an additional 23 specific amino acid residues which would have not been obvious in light of SEQ ID NO: 2 or the general description provided by the specification, the claims with SEQ ID NOs specifically claimed and are not fully supported in the provisional application 60/127,452, filed April 1, 1999.

Specification

The disclosure objected to because it contains an embedded hyperlink and/or other form of browser-executable code and because the specification makes reference to specific figures which are not present in the present disclosure is withdrawn.

The amendments to the specification have obviated the basis of the objection.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 47, 49-50, 52-54, 56-61 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn.

The amendments to the claims has obviated the basis of each of the specific rejections.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 52, 54, 60 and 61 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicants note that the specification provides 8 mutants of PAMP and describes the activity of the mutants relative affect on PAMP activity. Applicants argue that the artisan in possession of the wild type sequence and the mutant sequences could easily derive nucleic acid sequences encoding the same protein. Reviewing the evidence provided in the working

examples Applicants argue that each of the mutants are within the 90% identity range and all have the capability of binding presenilin, though in some cases at a reduced affinity. Using programs such as BLAST or FASTA algorithms it is argued that the artisan can easily envision sequence which are 90% identical and have the capability of interacting with presenilin. See Applicants amendment, pages 15-17. Applicants' arguments have been fully considered, but not found persuasive.

It is noted that claim 52 has been amended to recite that the sequence is 90% identical (from 60% identity) to SEQ ID NO: 14 and that the specification teaches eight mutant forms of PAMP. However, it should be noted that human PAMP, as set forth in SEQ ID NO: 14, is 709 amino acids in length. Importantly, each of the point mutants represent alterations of 0.1% identity change. The two deletion mutants which demonstrate reduced binding to presenilin represent identity changes of 4-8%. Further, beyond the description of the affects of the mutants, the specification provides no clear teaching to specifically what amino acids must be maintained or which can be changed without having affect on activity. As state in the previous office action, the courts have stated that: 'The written description requirement can be met by "showing that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics...i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with known or disclosed correlation between function and structure, or some combination of characteristics. *Enzo Biochem, Inc. v. Gen-Probe Inc.*, 296 F 3d at 1324, 63 USPQ2d at 1613 (Fd Cir 2002).

With respect to a complete description by identifying relevant characteristics, the specification fails to provide adequate structure-function analysis of the PAMP sequence wherein the artisan would readily know which amino acids can or can not be changed with out affecting the function of the resulting protein. Clearly the two deletion mutants demonstrate 4% and 8% of the protein can be removed, however in both cases the activity of PAMP is greatly reduced. Importantly, there is no teaching that greater deletions would not completely abolish the activity. Moreover, these are two simple deletions in the same region of the protein, while the claims encompass an enormous number of larger deletions throughout the entire protein, as well as insertions and point mutations scattered throughout as long as they are limited to producing a protein which is 90% identical. Additionally, as indicated in the previous office action, this functional language recited and relied upon in the claim 'capable of interacting with a presenilin' relates to the PAMP protein, not the polynucleotide which is instantly claimed. Therefore, this limitation does not describe the polynucleotide which is claimed, rather it describes one property of the PAMP protein encoded by SEQ ID NO: 13. The specification only provides a general outline which can be applied to any protein, and is silent with respect to any specific changes to the PAMP protein. Again, the functional limitations recited in the claim are directed to the protein produced and not the polynucleotide which is claimed. While one may be able to produce variant PAMP proteins from an altered SEQ ID NO 13 polynucleotide sequence, such is not at issue. What is at issue is whether the specification as filed, provides adequate written description of such polynucleotides or variant PAMP polypeptides encoded by a polynucleotide.

Accordingly, indicating generally that a variant protein maintains a property of the parent protein generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material.

Finally, while the artisan can make variant PAMP proteins and test the variants for a specific properties, however this is not sufficient to meet the written description requirement. The courts have stated that adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of identifying it. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991). Therefore, while one may make and test all the possible variant sequences encompassed by the claim, the specification fails to provide the necessary description to which of all these possible variants would retain any function of the parent molecule.

Thus, given the limited disclosure in the specification is not deemed sufficient to reasonably convey to one skilled in the art that Applicants were in possession of the huge genera recited and encompassed by the claims at the time the application was filed, and it is maintained that the written description requirement under 35 U.S.C. 112, first paragraph, is not satisfied for the claimed genera.

Dependent claims 54, 60, 61 are included in the basis of the rejection because they are drawn to products and methods which require mutant variant PAMP sequences.

Claims 52, 54, 60 and 61 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for making and using SEQ ID NO: 14, does not reasonably provide enablement for making and using any other functional variant of SEQ ID NO: 14. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Applicants summarize the basis of the rejection and argue that the specification not only provides general guidance, but specific guidance for PAMP pointing to page 41, lines 13-19. Further, the working examples describe eight variants, noting PAMP variants both decrease and increase PAMP function. Finally, Applicants argue that it would be routine experimentation to provide sequence variants and test them by co-precipitation assays for activity, citing *In re Wands* in support of their arguments. See Applicants amendment, pages 18-20. Applicants' arguments have been fully considered, but not found persuasive.

Initially, while screening a large number of cloned cell lines generated in a single step is routine as the courts found in *Wands*, the generation of enormous number of protein mutants with 10% variation introduced as encompassed by the claim is not. Further, even if a representative number of alterations could be made, the screening of all the mutants by co-immunoprecipitation assays would not be considered routine. In this case while methodology contemplated for testing may be conventional, it is not routine to perform the assay on the scale which would be necessary to make or use the full breadth of the claim. With respect to the specific guidance pointed to in

the specification (page 41 and working examples), it is noted that previous experiments indicate that the PS1/PS2-binding domain may be in the TM domain **or** the C-terminus of PAMP. However, the specification also provides no teachings on what specific amino acid sequence modifications, e.g. insertions, deletions and substitutions, would be permissible in a variant polypeptide that would improve or at least would not interfere with the biological activity or structural features necessary for the biological activity and stability of the protein. More importantly, as set forth in the previous office action, it is known in the art that even conservative amino acid substitutions can adversely affect proper folding and biological activity if amino acids that are critical for such functions are substituted, and the relationship between the sequence of a polypeptide and its tertiary structure is neither well understood nor predictable (see Ngo, in The Protein Folding Problem and Tertiary Structure Prediction, Merz *et al.* (eds.), Birkhauser Boston: Boston, MA, pp. 433 and 492-495, 1994). Rudinger (in Peptide Hormones, Parsons (ed.), University Park Press: Baltimore, MD, pp. 1-7, 1976) discloses that even for peptide hormones, which are much smaller than the instant lipase protein, one cannot predict variant amino acid sequences for a biologically active polypeptide. Rather one must engage in "case to case painstaking experimental study" to determine active variants (see page 7). Consequently, excessive trial and error experimentation would have been required to identify the necessary nucleic acid sequence derivatives encoding a biologically active lipase with an amino acid sequence differing from SEQ ID NO: 14 since the amino acid sequence of such polypeptides could not be predicted.

The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of proteins broadly encompassed by the claims and the claims broadly encompass a significant number of inoperative embodiments. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which can be tolerated in a protein's amino acid sequence and still retain similar biological activity requires a (1) knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which re conserved (*i.e.*, expectantly intolerant to modification), and (2) detailed knowledge of the ways in which the protein's structure relates to its function. However, as discussed above, the problem of predicting protein structure from mere sequence data of a single protein and in turn utilizing predicted structural determination to ascertain functional aspects of the protein and finally what changes can be tolerated with respect thereto is extremely complex and well outside the real of routine experimentation.

With respect to the 8 variants Applicants point to in the specification, it is maintained that this is only a small fraction of the enormous number of species encompassed by the claims. SEQ ID NO: 14 is 709 amino acids in length, an by way of example a smaller polypeptide chain of 100 amino acids would constitute 10^{130} possible combinations and as set forth in the previous office action "just one molecule of each of these different proteins would fill the entire [known] universe 10^{27} times over, even if packed together in the most efficient manner" (see paragraph 1, page 94 Creighton). Even if substitutions with the natural 20 amino acids encoded by DNA were

the only modifications, instant claims would still broadly encompass a multitude of species; calculated as 20N * (length)!/N/(length-N)! wherein "20" is the number of natural amino acids encoded by DNA, "N" is the number of positions where substitutions can occur, "!" is the factorial symbol, "/" is the division symbol and "length" is the total number of amino acids in the protein or peptide. In putting these numbers in perspective, it is noted that the earth is estimated to have existed for 10^{17} seconds (see Creighton, T.E. 1983. Proteins: Structure and Molecular Principles, W. H. Freeman and Company, NY. 93-94, page 94, paragraph 1). Therefore, while recombinant and mutagenic techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications of other types and the positions within the protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining similar biological activity are limited in any protein. The result of such modifications is unpredictable based on the instant disclosure. One skilled in the art would expect any tolerance to modification shown for a given protein to diminish with each further and additional modification, e.g., multiple substitutions. The sequence of some proteins is highly conserved and one skilled in the art would not expect tolerance to any amino acid modifications in such proteins.

Thus, the specification has not provided sufficient guidance to enable one of skill in the art to make and use the claimed protein in a manner reasonably correlated with the scope of the claims, broadly including any number of additions, deletions, or substitutions and fragments of any size. The situation at hand is analogous to that in *Genentech v. Novo Nordisk A/S* 42

USPQ2d 1001. Given the art recognized unpredictability conserving function when altering amino acid sequences, the lack of specific guidance for alterations in PAMP which would result in a functional variant or fragment, and the enormous number of possible variants encompassed by the claims which the artisan must test, it would have required undue experimentation to make and/or use the invention as claimed.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 52 stands rejected under 35 U.S.C. 102(b) as being anticipated by Genbank Accession Number D87442.

Initially, with respect to claims 47, 49, 50 and 53, the amendments to the claims have obviated the claimed invention form that previously disclosed, and the rejection is withdrawn over these claims.

With respect to claim 52, Applicants note the amendment to the claim and argue that the vector could not encode a protein which would interact with presenilin. More specifically, Applicants point to MPEP 2121.02 and argue that because the sequence of Genbank Accession

Number D87442 does not provide an enabled disclosure because it is out of frame, and that any resulting protein made with the vector would not have the ability to interact with presenilin. See Applicants amendment, pages 21-22. Applicants arguments has been fully considered, but not found persuasive.

Upon review of newly amended claim 52, Examiner would agree that the vector comprises "a nucleic acid encoding PAMP having at least 90% amino acid identity to SEQ ID NO: 14" and the PAMP protein encoded by said sequence is "capable of interacting with a presenilin" (claim 52), however, there is no requirement in the claim that the cell or the vector produce the protein. Claim 52 encompasses a cell containing any sequence which has 90% identity to SEQ ID NO 14 and encodes a protein which interacts with presenilin. As noted in the previous office action, the encoding polynucleotide sequence of Genbank Accession Number D87442 is 99.9% identical, in particular over the domain that which interacts with presenilin. Therefore, each of the limitations set forth in the claim are met, an isolated cell containing a vector comprising a polynucleotide encoding PAMP. Whether the cell produces the protein is immaterial because the claim does not recite or require this limitation.

Conclusion

Claims 47, 49, 50, 56-59 are allowed. Claims 63 and 65 are objected to for being dependent on rejected claims but would be found allowable if rewritten as independent claims

encompassing the embodiments of the independent claim and any intervening claims. Claims 54, 60 and 61 are free of the art of record, however they are subject to other rejections.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joseph Woitach whose telephone number is (703)305-3732.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached at (703)305-4051.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group analyst Dianiece Jacobs whose telephone number is (703) 308-2141.

Joseph T. Woitach

Deborah Crouch

DEBORAH CROUCH
PRIMARY EXAMINER
GROUP ~~1800~~ 1630